The Application of Three-dimensional Ultrasonography in the Prenatal Diagnosis of Arthrogryposis

I-Wen Lin, Ho-Yen Chueh, Shuenn-Dyh Chang, Po-Jen Cheng*

Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital, Linkou Medical Center, and College of Medicine, Chang Gung University, Taoyuan, Taiwan.

SUMMARY

Objective: To present the application of three-dimensional (3D) ultrasonography in the early prenatal diagnosis of fetal arthrogryposis.

Case Report: A 26-year-old multipara had a fetus with anomalies of the limbs as shown by conventional ultrasonography at 18 weeks of gestation. A follow-up 3D ultrasonogram at the same gestational age was consistent with the diagnosis of arthrogryposis. Based on an abnormal chromosome 18p on the fetal karyotype, termination of the pregnancy was performed at 22 weeks' gestation. The outward appearance of the fetus coincided with the prenatal sonographic findings of arthrogryposis.

Conclusion: As an advanced and sophisticated technology, 3D ultrasonography can serve as a useful technique for the early diagnosis of fetal anomalies, including arthrogryposis. The earlier the diagnosis is established, the earlier the appropriate management can be initiated, including counseling, additional work-up and timely termination of pregnancy, if indicated. [*Taiwan J Obstet Gynecol* 2008;47(1):75–78]

Key Words: arthrogryposis, prenatal diagnosis, three-dimensional ultrasonography

Introduction

Arthrogryposis (arthrogryposis multiplex congenita) describes a spectrum of congenital muscle disorders, leading to non-progressive multiple joint contractures at birth [1–3]. Frequently, the contractures are accompanied by muscle weakness, which further limits movement. The affected joints range from the hands, wrists, elbows, shoulders, hips, feet, and knees in the classic form of the condition; nearly every body joint, including the jaw and back, is involved in the most severe cases of arthrogryposis.

There is a scarcity of literature regarding the prenatal diagnosis of arthrogryposis, although an early suspected diagnosis has never been established by ultrasound. The few sonographic findings that were noted included malposition of the limbs, increased nuchal edema, and polyhydramnios. Herein, we present the first reported case of the prenatal diagnosis of fetal arthrogryposis with the application of three-dimensional (3D) ultrasonography.

Case Report

A 26-year-old, gravida 3, para 1, abortus 1, female patient attending our prenatal clinic was shown by conventional ultrasonography at 18 weeks' gestation to have a fetus with suspected limb anomalies. Her first pregnancy resulted in the vaginal delivery of a healthy female one year previously. A further detailed 3D ultrasonographic evaluation done using Voluson 730 Expert system (GE Medical Systems, Kretztechnik, Zipf, Austria) with 5- and 7-MHz transabdominal transducers on the fetus disclosed the following findings, all of which

*Correspondence to: Dr Po-Jen Cheng, Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital, Linkou Medical Center, 5, Fusing Street, Gueishan, Taoyuan 333, Taiwan.
E-mail: pjcheng@cgmh.org.tw
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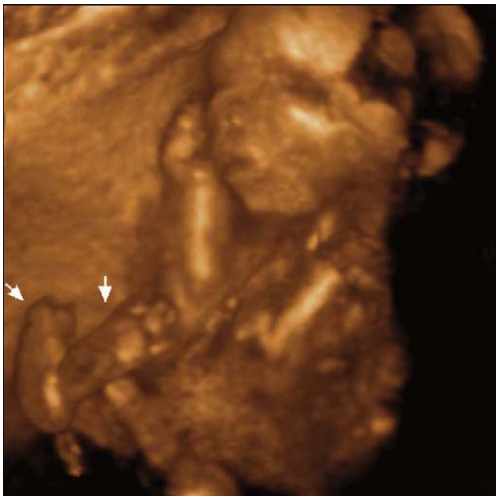

Figure 1. Clubfoot (arrow).

Figure 3. Hip joints bending upward stiffly (arrow) and straight knee joints (arrowhead) under maximal translucent mode.

Figure 2. Straight knee joints (arrow).

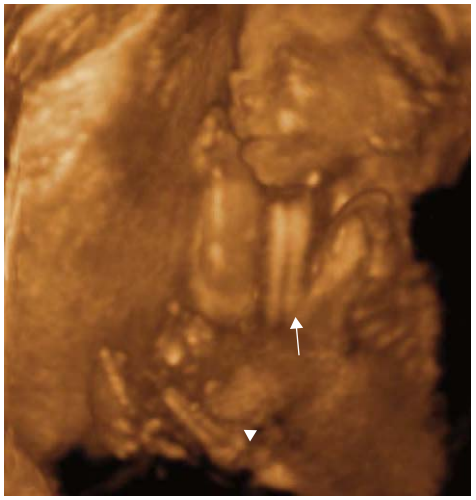

Figure 4. Elbows bending up stiffly (arrow) and straightened knees (arrowhead). Note the same position of the fetus as in Figure 2.

were suggestive of arthrogryposis: clubfoot (Figure 1), straight knees (Figure 2), and hip joints bending up stiffly that did not change position over time (Figures 3 and 4; Figure 4 acquired via maximal translucent mode).

Except for being a carrier of hepatitis B, the patient denied any systemic diseases, including myasthenia gravis or other immunologic disorders, nor did she recall any hereditary problems in her close or distant relatives. The patient underwent a series of assessments. The TORCH (*Toxoplasma gondii*, rubella virus, cytomegalovirus, and herpes simplex virus), IgM titers and anti-acetylcholine antibody titers for suspected myasthenia gravis were all negative. The fetal karyotype revealed a *de novo* chromosome 18p anomaly of male gender, with rearrangement occurring at the distal end of the short arm of chromosome 18. Both parents had a normal chromosomal constitution.

After prenatal genetic counseling, the parents decided to undergo termination of the pregnancy at 22 weeks of gestation. Extraovular induction of labor with intrauterine placement of an inflated Foley balloon catheter (22F) and intravaginal prostaglandin E2 (Prostin) was applied. Within 18 hours, the fetus and placenta were delivered spontaneously. Further molecular cytogenetic analysis (i.e. fluorescence *in situ* hybridization) to characterize the abnormal 18p chromosome was compromised because of contamination of the fetal tissue and cord blood during the specimen collection procedure. Nevertheless, grossly, the fetus appeared very similar to the 3D ultrasound image (Figures 5 and 6). The final anatomic diagnoses via autopsy included: bilateral clubfoot, genu valgus, low-set ears, bilateral undescended testes, and extramedullary hematopoiesis of the liver and spleen.

Figure 5. Gross picture of the abortus (lateral view).

Figure 6. Gross picture of the abortus (frontal view).

Discussion

Arthrogryposis encompasses a number of syndromes and sporadic deformities that are individually rare, occurring in approximately 1 in 3,000 births, but are not uncommon when grouped together. In about 30% of the cases, a genetic cause is identified [4], which would be related to the risk of recurrence. Our case had a *de novo* chromosomal 18p abnormality (Figure 4), but contamination of fetal tissue and blood during the specimen collection procedure precluded further molecular cytogenetic characterization of the defect. In the early 1990s, chromosome X had been reported to be linked to arthrogryposis [5–7], especially in its lethal form; recently, the literature has implicated chromosome 5qter in connection with the neuropathic form [8–10]. In general, the causes of arthrogryposis are classified as extrinsic, such as oligohydramnios and uterine anomalies, and intrinsic, such as musculoskeletal, neuromuscular, neurologic and connective tissue factors [11]. The case described herein had a chromosome distal 18p rearrangement anomaly; there was no other specific cause identified by corollary studies nor was a hereditary association in the family disclosed.

One characteristic feature of arthrogryposis is dimples near the affected joints, which suggest contact between the skin and bone during the early stages of pregnancy. Because many joint spaces have formed by the seventh week of gestation, and folds appear in the skin by the 11th week of gestation, this characteristic feature provides an indication as to when the disability is caused during pregnancy. Research using animal models has shown that prevention of fetal movement at 10–12 weeks of gestation induces fixed joints. The continuous movement of a fetus is thus necessary for normal growth of the limbs and joints. If an *in utero* insult stops joint movement, even transiently, the joints become stiff and it is difficult for the fetus to stretch and resume normal movement.

Regarding the prenatal diagnosis of arthrogryposis via ultrasonography [12], the hallmark observation was scant or absent motion of fetal extremities [13,14]. In recent studies, the focus has been on bone anomalies, such as osseous heterotopias [15] and osteopenia [16], to arrive at a more specific diagnosis of arthrogryposis during the prenatal period. In addition, cystic hygroma [17] or increased nuchal translucency, especially in lethal cases [18,19], combined with the detection of diminished fetal movements and joint contractures, may lead to an early diagnosis of suspected arthrogryposis in the first trimester.

In contrast to conventional two-dimensional (2D) ultrasonography, 3D ultrasonography may better delineate the abnormal positions of the fetal limbs and arms in stereographic pictures and therefore may be used as a confirmatory method of evaluation by providing clear and detailed images of the sequence. Real-time 3D ultrasonography allowed us to show that these postural abnormalities were fixed, with no fetal movements. In cases with arthrogryposis, Ruano et al [20] first reported that 3D ultrasonography showed the fixed postural abnormalities of the fetal extremities and body, especially in the skeletal mode, which were confirmed by postmortem examinations. Furthermore, these images, which illustrate the ever-increasing quality and discrimination of 3D ultrasonography, may be helpful for parents in understanding the characteristics of the postural abnormalities, thus improving prenatal counseling. Our 3D ultrasonography images disclosed very specific findings in the fetus with arthrogryposis, including extremity joints bending stiffly upward, overlapping fingers, and clubfoot, coinciding with those of

the published report [20]. As to the maximal translucent mode, it could reveal more detailed and clearer the relative position of bones adjacent to the joints of limbs. Via the maximal translucent mode, the resultant ultrasonographic picture was just like the one of radiography. Owing to the early prenatal suspected diagnosis of arthrogryposis made by 3D ultrasonography, which is more detailed compared with findings on 2D ultrasonography, various follow-up managements were initiated early, including counseling, performing other tests and the timely termination of the pregnancy.

In conclusion, obstetric ultrasonography plays a significant role, like a sentinel, in the prenatal diagnosis of fetal anomalies; many other confirmatory tests may follow thereafter. As the technology becomes more advanced and sophisticated, the diagnosis can be made at an earlier prenatal period and with better accuracy.

References

1. Hall JG. Arthrogryposis multiplex congenita: etiology, genetics, classification, diagnostic approach, and general aspects. *J Pediatr Orthop B* 1997;6:159–66.
2. Gordon N. Arthrogryposis multiplex congenita. *Brain Dev* 1998;20:507–11.
3. Mennen U, van Heest A, Ezaki MB, Tonkin M, Gericke G. Arthrogryposis multiplex congenita. *J Hand Surg [Br]* 2005; 30:468–74.
4. Hall JG. Genetic aspects of arthrogryposis. *Clin Orthop Relat Res* 1985;194:44–53.
5. Hennekam RC, Barth PG, Van Lookeren Campagne W, De Visser M, Dingemans KP. A family with severe X-linked arthrogryposis. *Eur J Pediatr* 1991;150:656–60.
6. Kobayashi H, Baumbach L, Matise TC, Schiavi A, Greenberg F, Hoffman EP. A gene for a severe lethal form of X-linked arthrogryposis (X-linked infantile spinal muscular atrophy) maps to human chromosome Xp11.3–q11.2. *Hum Mol Genet* 1995;4:1213–6.
7. Zori RT, Gardner JL, Zhang J, et al. Newly described form of X-linked arthrogryposis maps to the long arm of the human X chromosome. *Am J Med Genet* 1998;78:450–4.
8. Shohat M, Lotan R, Magal N, Shohat T, Fischel-Ghodsian N, Rotter JI, Jaber L. A gene for arthrogryposis multiplex congenita neuropathic type is linked to D5S394 on chromosome 5qter. *Am J Hum Genet* 1997;61:1139–43.
9. Tanamy MG, Magal N, Halpern GJ, Jaber L, Shohat M. Fine mapping places the gene for arthrogryposis multiplex congenita neuropathic type between D5S394 and D5S2069 on chromosome 5qter. *Am J Med Genet* 2001;104:152–6.
10. Genini S, Malek M, Spilar S, et al. Arthrogryposis multiplex congenita (AMC), a hereditary disease in swine, maps to chromosome 5 by linkage analysis. *Mamm Genome* 2004; 15:935–41.
11. Swinyard CA, Bleck EE. The etiology of arthrogryposis (multiple congenital contracture). *Clin Orthop Relat Res* 1985; 194:15–29.
12. Gorczyca DP, McGahan JP, Lindfors KK, Ellis WG, Grix A. Arthrogryposis multiplex congenita: prenatal ultrasonographic diagnosis. *J Clin Ultrasound* 1989;17:40–4.
13. Baty BJ, Cubberley D, Morris C, Carey J. Prenatal diagnosis of distal arthrogryposis. *Am J Med Genet* 1988;29:501–10.
14. Dudkiewicz I, Achiron R, Ganel A. Prenatal diagnosis of distal arthrogryposis type 1. *Skeletal Radiol* 1999;28:233–5.
15. Gullino E, Abrate M, Zerbino E, Bricchi G, Rattazzi PD. Early prenatal sonographic diagnosis of neuropathic arthrogryposis multiplex congenita with osseous heterotopia. *Prenat Diagn* 1993;13:411–6.
16. Murphy JC, Neale D, Bromley B, Benacerraf BR, Copel JA. Hypoechogenicity of fetal long bones: a new ultrasound marker for arthrogryposis. *Prenat Diagn* 2002;22:1219–22.
17. Scott H, Hunter A, Bedard B. Non-lethal arthrogryposis multiplex congenita presenting with cystic hygroma at 13 weeks gestational age. *Prenat Diagn* 1999;19:966–71.
18. Hyett J, Noble P, Sebire NJ, Snijders R, Nicolaides KH. Lethal congenital arthrogryposis presents with increased nuchal translucency at 10–14 weeks of gestation. *Ultrasound Obstet Gynecol* 1997;9:310–3.
19. Madazli R, Tuysuz B, Aksoy F, Barbaros M, Uludag S, Ocak V. Prenatal diagnosis of arthrogryposis multiplex congenita with increased nuchal translucency but without any underlying fetal neurogenic or myogenic pathology. *Fetal Diagn Ther* 2002;17:29–33.
20. Ruano R, Dumez Y, Dommergues M. Three-dimensional ultrasonographic appearance of the fetal akinesia deformation sequence. *J Ultrasound Med* 2003;22:593–9.